

### REMARKS

Any fees that may be due in connection with the filing of this paper or with this application should be charged to Deposit Account No. 02-1818. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 1-11, 37-40 and 42-57 are pending. Claims 54-57 are added herein. Basis for claims 54-57 is found, *e.g.*, at page 8, line 9 and in original claim 20. No new matter has been added.

### REJECTION OF CLAIMS UNDER 35 U.S.C. 103(a)

#### A. Hechter, Schiller and Fukahori *et al.*

Claims 1-7, 9, 10, 37, 38, 40, 42, 44, 46, 48, 50 and 52 are rejected under 35 U.S.C. 103 (a) as unpatentable over Hechter (US 4,975,286) in view of Schiller (Aliment Pharmacol Ther 15: 749-763 (2001)) and Fukahori *et al.* (JP 07242539) because Hechter allegedly teaches every element of the claims except the use of a minimally degradable sugar, but the teachings of Schiller and Fukahori *et al.* allegedly cure this defect. The Examiner alleges that Schiller teaches that osmotic agents can be used to treat constipation and that lactulose or sugar alcohols, such as sorbitol or mannitol, are osmotic agents. The Examiner alleges that Fukahori *et al.* teaches compositions that have laxative effect, and that the compositions include a sugar alcohol, such as xylitol, sorbitol, mannitol, maltitol or isomaltitol. The Examiner alleges that it would have been obvious to one of ordinary skill in the art to have combined the teachings of Hechter, Schiller and Fukahori *et al.* and to have added xylose as a minimally degradable sugar in the composition of Hechter. The Examiner concludes that it would have been obvious to the ordinarily skilled artisan to have combined two or more compositions useful for the same purpose in order to form a third composition that is to be used for the very same purpose.

Reconsideration of the grounds for the rejection respectfully is requested in view of the following remarks.

### THE CLAIMS

Claim 1 recites a purgative composition of that contains (i) at least one water-soluble sodium salt; (ii) at least one water-soluble minimally degradable sugar, where the total weight of water-soluble minimally degradable sugar in the composition is from about 1 to about 3 times the weight of sodium salt in the composition; (iii) at least one water-soluble potassium salt, where the weight of the water-soluble potassium salt in the composition is from about

0.05 to about 1 times the weight of the sodium salt in the composition; and (iv) at least one water-soluble magnesium salt, where the weight of magnesium salt in the composition is from about 0.1 to about 10 times the weight of sodium salt in the composition. Claims 2-7, 9, 10, 37, 38, 40, 42, 44, 46, 48, 50 and 50 ultimately depend from claim 1 and include every limitation thereof.

**The teachings of the cited art and differences from the claimed subject matter**

**Hechter**

Hechter teaches an isotonic cathartic solution that contains about 3.5 grams/liter of sodium sulfate, about 4.82 grams/liter of magnesium sulfate, about 1.9 grams/liter of sodium bicarbonate, about 3.85 grams/liter of sodium chloride and about 0.746 grams/liter of potassium chloride. Hechter teaches that its composition contains no organic matter because the organic constituents used in some prior art cathartics, when metabolized, can create explosive gases that have exploded during certain procedures, causing death to the patients (see col. 1, lines 33-36). Hechter teaches that because its composition does not include such organic materials, it does not result in potentially explosive gases (col. 4, lines 37-39).

**Schiller**

Schiller reviews the theory and treatment of constipation. Schiller teaches that osmotic agents can be used as laxatives, and that their mechanism of action is to reduce fluid absorption by the intestine by providing poorly absorbed osmotically active substances that hold additional water intraluminally (page 750, last paragraph). Schiller teaches that lactulose, sorbitol and mannitol are poorly absorbed osmotic agents that are used as laxatives (page 751, Table 2). Schiller teaches that bacterial breakdown of the minimally degradable sugar lactulose by bacteria in the colon produces gas, including hydrogen, and that sufficient gas may remain in the intestine to produce distension, bloating and excess flatus and may limit the use of this osmotic agent (page 753, col. 2, second full paragraph). Schiller teaches that sorbitol is similar to lactulose in its propensity to produce gas (paragraph bridging pages 753-754). Schiller teaches that lactulose or other fermentable substrates should not be used for gastrointestinal lavage for colon preparation because of the risk of producing hydrogen gas in explosive concentrations in the colon (page 759, col. 1, second full paragraph).

**Fukahori *et al.***

Fukahori *et al.* describes compositions that provide a laxative effect, where the compositions include an amount of sugar alcohol, insufficient by itself to provide a laxative effect, combined with an organic acid, such as citric acid, succinic acid, lactic acid, fumaric

acid maleic acid, acetic acid or tartaric acid. The reference alleges that there is a synergistic action between the organic acid and the sugar alcohol that produces a laxative effect. An exemplary composition is described as containing 8000 mg reduced starch hydrolysate (which contains 1-5% sorbitol, 50-55% maltitol, 17-25% maltotritol (a hydrogenation product of maltotriose), and 23-30% oligosaccharide alcohol), 2000 mg 50% lactic acid and 2000 mg citric acid in 100 mL water with 50 mg sodium benzoate.

#### ANALYSIS

It respectfully is submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

#### **The combination of the teachings of Hechter and Schiller and Fukahori *et al.* does not result in the claimed compositions and methods**

The Examiner states that Hechter does not teach or suggest the use of a minimally degradable sugar, but alleges that the teachings of Schiller and Fukahori *et al.* cure this defect. Applicant respectfully disagrees. Hechter teaches that its composition contains no organic matter because the organic constituents used in some prior art cathartics, when metabolized, can create explosive gases that have exploded during certain procedures, resulting in death. Hechter teaches that because its composition does not include such organic materials, there is no problem with the development of potentially explosive gases. Hence, according to the teachings of Hechter, inclusion of organic matter would result in a composition that would produce explosive gases when used as a purgative. Thus, in light of the teachings of Hechter, the modification of the Hechter composition proposed by the Examiner would render it unsatisfactory, due to the alleged undesirable side-effect taught by Hechter, since a minimally degradable sugar is organic matter (and as already made of record, it is known in the art that mannitol, which is a minimally degradable sugar, is not used in purgative compositions due to the hydrogen and methane gas produced by the decomposition of the mannitol by the bacteria in the intestines and the possible explosion of the intestines during operations due to these gases – see Kawakami, JP 05306221, paragraph [00005]). Thus, there can be no suggestion or motivation to have made the proposed modification (*In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)), since such modification is taught by Hechter to be undesirable. Therefore, the teachings of the references cannot render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

This is further supported by the teachings of Schiller, which teaches that lactulose or other fermentable substrates should not be used for gastrointestinal lavage for colon preparation because of the risk of producing hydrogen gas in explosive concentrations in the colon. Schiller teaches that sorbitol, a minimally degradable sugar alcohol, has the same propensity to produce explosive gases as lactulose. Thus, in light of the teachings of Hechter and Schiller, the modification of the Hechter composition proposed by the Examiner to include a minimally degradable sugar would render the composition unsatisfactory, due to the alleged undesirable side-effect taught by Hechter and Schiller.

The teachings of Fukahori *et al.* do not cure this defect. Fukahori *et al.* teaches that a sugar alcohol can be combined with an organic acid to provide a laxative effect for the treatment of constipation. There is no teaching or suggestion that its composition is suitable for use as a purgative. Fukahori *et al.* was published in 1995, and thus predates the teachings of Schiller, which teaches that fermentable substrates should not be used for gastrointestinal lavage for colon preparation.

None of Hechter, Schiller or Fukahori *et al.*, alone or in any combination, teaches or suggests a composition that contains, or would lead one of ordinary skill in the art to modify the composition of Hechter so that it contains, a minimally degradable sugar in an amount that is about 1 to about 3 times the weight of sodium salt in the composition; and contains an amount of water soluble potassium salt in an amount that is about 0.05 to about 1 times the weight of the sodium salt in the composition; and contains an amount of water soluble magnesium salt in an amount that is about 0.1 to about 10 times the weight of sodium salt in the composition. Therefore, for at least these reasons, the combination of the teachings of Hechter, Schiller and Fukahori *et al.* does not teach or suggest every element of the compositions of claims 1-7, 9, 37, 38, 42, 44 and 46 or the methods of claims 10, 48, 50 and 52 or any pending claim. Added claims 54 and 56 are composition claims that ultimately depend from claim 1 and incorporate every limitation thereof. Added claims 55 and 57 are method claims that include as an element administration of a compound of claim 1 or claim 8. Thus, for the same reasons set forth above, the combination of the teachings of Hechter, Schiller and Fukahori *et al.* also fails to teach or suggest every element of the compositions of claims 54 and 56 and the methods of claims 55 and 57. Therefore, the combination of the teachings of Hechter, Schiller and Fukahori *et al.* does not render any of claims 1-7, 9, 10, 37, 38, 40, 42, 44, 46, 48, 50, 52 and 54-57 or any pending claim *prima facie* obvious.

## DECLARATIONS

**Notwithstanding the above, the Declarations of Dr. Borody already of record demonstrate results not taught or suggested by the cited art.**

The primary reference, Hechter, describes aqueous cathartic solutions that include about 3.5 g/L sodium sulfate; about 4.82 g/L magnesium sulfate; about 1.9 g/L sodium bicarbonate, about 3.85 g/L sodium chloride and about 0.746 g/L potassium chloride prepared as an isotonic solution that is substantially free of organic components. Hechter teaches that its solution is isotonic so that it has little effect on blood physiology, osmolarity, pH and ion concentrations. Hechter teaches that its composition contains no organic components because the organic constituents used in some prior art cathartics, when metabolized, can create explosive gases that have exploded during certain procedures, causing death to the patients. As discussed above, Schiller specifically teaches that fermentable sugars, such as lactulose or sorbitol (which are minimally degradable sugars), should not be used for gastrointestinal lavage because they can result in the production of hydrogen gas in explosive concentrations in the colon. Thus, minimally degradable sugars, such as lactulose and sorbitol, are "organic components" as described in Hechter, since the art teaches these compounds can create explosive gases when metabolized.

In addition to containing the water-soluble sodium, potassium and magnesium salts in the recited ratios, the instant compositions also include at least one water-soluble minimally degradable sugar. Thus, the instantly claimed compositions include "organic components" as that phrase is used in Hechter. The DECLARATIONS already of record demonstrate that the presence of minimally degradable sugars in the instant compositions does not result in the production of explosive gases. For example, in the second DECLARATION of Dr. Borody, submitted with the Response filed March 15, 2010, the use of minimally degradable sugars avoids the gas formation, bloating and cramps that can be caused by easily degradable sugars such as sucrose (see page 3). The Clinical Study Report, provided with the first DECLARATION of Dr. Borody, submitted with the Response filed June 26, 2009, teaches that compositions within the scope of the instant claims resulted in no bloating, which is usually attributable to gas formation (see page 32 of the report). Hence, the purgative compositions as instantly claimed provide effective cleansing of the colon and do not result in explosive gas formation. Thus, contrary to the teachings of the prior art, including a minimally degradable sugar in the purgative compositions as instantly claimed does not result in explosive gas formation.

Compositions within the scope of claim 1 and its dependent claims containing different minimally degraded sugars resulted in enhanced colon cleansing. As discussed in the second DECLARATION of Dr. Borody, provided with the Response, filed March 15, 2010, the compositions containing mannitol and xylose exhibited enhanced bowel cleansing compared to standard PicoPrep™ compositions, which do not include a minimally degradable sugar. Compositions within the instant claims that included inulin also demonstrated enhanced purgative properties similar to those observed with compositions that contain mannitol. Thus, purgative compositions within the scope of the instant claim 1 and its dependent claims that include minimally degradable sugars of various classes, including monosaccharide (xylose), oligosaccharide (inulin) and sugar alcohols (mannitol), exhibit enhanced bowel cleansing with no reported explosive gas formation. Thus, the results are unexpected in light of the teachings of the art.

**B. Hechter, Schiller, Borody *et al.* and Jacob *et al.***

Claims 1-11, 37-40, and 42-53 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Hechter and Schiller in view of Borody *et al.* (US 5,858,403), and Jacob *et al.* (US 6,162,464), because Hechter allegedly teaches every element of the claims except formulating in a tablet form or the use of picosulfate, but Schiller, Borody *et al.* and Jacob *et al.* allegedly cure these defects. Borody *et al.* allegedly teaches an osmotic colonic evacuant in solid dosage form, such as a tablet, that contains a phosphate-based or sulfate-based laxative, sodium picosulfate and an antacid. Borody *et al.* allegedly teaches that the solid oral dosage form is coated to avoid dissolution in the mouth. Jacob *et al.* allegedly teaches orally administered colonic purgative formulations containing non-aqueous admixtures of purgative salts including magnesium salts, sodium tartrate, potassium tartrate, and mixtures thereof, administered in tablet or capsule form. The Examiner alleges that it would have been obvious to one of ordinary skill in the art to have combined the teachings of Hechter, Schiller, Borody *et al.* and Jacob *et al.* and formulate the composition of Hechter into a tablet and to include sodium picosulfate. The Examiner alleges that an ordinarily skilled artisan would have been motivated to formulate the compositions of Hechter into tablet form because Borody *et al.* and Jacob *et al.* teach the formulation of colonic purgatives into tablet formulations to provide conveniently administered dosage formulations to improve patient compliance. The Examiner alleges that although none of the references teaches or suggests a tablet formulation having a core comprising sodium, potassium, and magnesium salts and a coating comprising a minimally degradable sugar, Borody *et al.* teaches coating purgative

compositions in tablet form to avoid dissolution in the mouth and thus it would have been obvious to the skilled artisan to use a coating over the core salts. The Examiner alleges that selection of the particular coating is a matter of routine experimentation and optimization and well within the purview of the ordinarily skilled artisan, and that absent evidence that the coating of the core of the purgative salts with a minimally degradable sugar provides unexpected results, such a coating would have been obvious to the ordinarily skilled artisan.

### **THE CLAIMS**

See related section above. Claim 47 recites a purgative composition of claim 1 in the form of a tablet, where the tablet includes a core containing the sodium, potassium and magnesium salts and a coating containing the minimally degradable sugar(s), where the coating surrounds the core.

### **The teachings of the cited art and differences from the claimed subject matter. Hechter and Schiller**

The teachings of Hechter and Schiller are discussed above. Hechter teaches that its composition contains no organic matter because the organic constituents used in some prior art cathartics, when metabolized, can create explosive gases that have exploded during certain procedures causing death to the patients. Hechter teaches that because its composition does not include such organic materials, there is no problem with the development of potentially explosive gases. Schiller teaches that lactulose or other fermentable substrates such as sugar alcohols like sorbitol should not be used for gastrointestinal lavage for colon preparation because of the risk of producing hydrogen gas in explosive concentrations in the colon.

### **Borody *et al.* (5,858,403)**

Borody *et al.* teaches an osmotic colonic evacuant that is provided in a solid dosage form, which contains a phosphate based laxative or a sulfate based laxative and can include a sodium picosulfate and an antacid, and is used to evacuate the colon, to treat small bowel bacterial overgrowth, irritable bowel syndrome, and acute or chronic bacterial bowel infections. There is no mention of including any minimally degradable sugar or any sugar in the solid dosage form. Borody *et al.* teaches that its tablet can be coated with a film to avoid dissolution in the mouth (col. 3, lines 62-63) but provides no teaching or suggestion as to the type of film that could be used. With respect to coatings, Borody *et al.* teaches that ascorbic acid may be coated with silicone or ethyl cellulose (col. 5, lines 26-27), neither of which is a minimally degradable sugar.

**Jacob *et al.* (US 6,162,464)**

Jacob *et al.* teaches orally administered colonic purgative formulations and methods of its use for effecting partial or complete purgation of the colon in mammals. The formulations consist of non-aqueous admixtures of a purgative salt selected from the group consisting of  $Mg_3(PO_4)_2$ ,  $MgHPO_4$ ,  $Mg(H_2PO_4)_2$ ,  $MgSO_4$ ,  $MgCl_2$ ,  $Na_2SO_4$ , sodium tartrate, potassium tartrate, magnesium tartrate and mixtures thereof in tablet or capsule form. Jacob *et al.* teaches that in preparations that depend on isotonicity for their effectiveness, addition of even the most common natural sweeteners such as glucose, fructose, saccharose, and sorbitol could change the osmolarity of these solutions and the inclusion of such adjuvants are generally expressly prohibited (col. 2, lines 36-40). Jacob *et al.* also teaches that it is well recognized in the art that the addition of appreciable quantities of substances that can be fermented by the intestinal flora should be avoided because of gas formation, which could be extremely dangerous (col. 2, lines 44-49). Thus, Jacob *et al.* does not teach or suggest a tablet that includes a minimally degradable sugar, such as sorbitol, nor a tablet that includes a coating containing minimally degradable sugar(s) surrounding a core.

**ANALYSIS**

It respectfully is submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

**The combination of the teachings of Hechter and Schiller and Borody *et al.* and Jacob *et al.* does not result in the claimed compositions and methods**

**Claims 1-11, 37-40, 42, 46 and 48-53**

In setting forth the rejection, the Examiner states (Page 8) that Hechter does not teach the formulation in tablet form or the use of picosulfate, and it is for this reason that Schiller, Borody *et al.* and Jacob *et al.* are added as secondary references.

Hechter teaches an isotonic cathartic solution of various salts. Hechter teaches that compositions containing "organic materials" as components can result in undesirable side-effects, including death of the patient, and its formulations avoid this by excluding organic materials. Thus, there can be no suggestion or motivation to have made the proposed modification of including a minimally degradable sugar in the compositions of Hechter, since such modification is taught by Hechter to be undesirable.

Schiller does not cure this defect. Schiller teaches that lactulose or other fermentable substrates, including sugar alcohols such as sorbitol should not be used for gastrointestinal lavage for colon preparation because of the risk of producing hydrogen gas in explosive



concentrations in the colon. Thus, the combined teachings of Hechter and Schiller would not lead one of ordinary skill in the art to modify the compositions of Hechter to include a fermentable substrate such as a minimally degradable sugar as instantly claimed.

Borody *et al.* is silent with respect to including any sugar in its formulation. Hence, Borody *et al.* provides no teaching or suggestion to include a minimally degradable sugar in a purgative composition. Thus, the combined teachings of Hechter, Schiller and Borody *et al.* would not lead one of ordinary skill in the art to modify the compositions of Hechter to include a fermentable substrate such as a minimally degradable sugar as instantly claimed.

Jacob *et al.* does not cure this defect. The composition of Hechter is an isotonic cathartic solution of various salts. Jacob *et al.* teaches that in cathartic preparations that depend on isotonicity for their effectiveness, addition of even the most common natural sweeteners, such as sorbitol, could change the osmolarity of these solutions and the inclusion of such sugars are generally expressly prohibited. Jacob *et al.* also teaches that it is well recognized in the art that the addition of appreciable quantities of substances that can be fermented by the intestinal flora should be avoided because of gas formation, which could be extremely dangerous.

Accordingly, since each of Hechter and Jacob *et al.* teaches that substances that can be fermented by the intestinal flora should be avoided in purgative compositions because of possibly extremely dangerous gas formation, and Schiller teaches that lactulose or other fermentable substrates, including sugar alcohols such as sorbitol, should not be used for gastrointestinal lavage for colon preparation because of the risk of producing hydrogen gas in explosive concentrations in the colon, there can be no suggestion or motivation to have made the modification proposed by the Examiner (*In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)), since such modification is taught by Hechter, Schiller and Jacob *et al.* to be undesirable. Thus, the teachings of the references cannot render any of claims 1-11, 37-40, and 42-53 or any pending claim *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). Therefore, for at least these reasons, the combination of the teachings of Hechter and Schiller and Borody *et al.* and Jacob *et al.* does not teach or suggest every element of any of claims 1-11, 37-40, 42, 46 and 48-53.

#### Claim 47

The Examiner states that Hechter does not teach or suggest a formulation in the form of a tablet or the use of picosulfate, but alleges that the secondary references cure these defects. Not only is there no mention of a solid dosage in the form of a tablet in Hechter, there is no

teaching or suggestion in Hechter to provide a purgative composition in the form of a tablet surrounded by a coating containing minimally degradable sugar(s). As discussed above, Hechter teaches that compositions containing "organic materials" as components can result in undesirable side-effects, including death of the patient. Thus, there can be no suggestion or motivation to include a minimally degradable sugar in a coating surrounding a tablet form of the compositions of Hechter, since including an organic material such as a minimally degradable sugar is taught by Hechter to be undesirable.

None of the secondary references cures this defect. Schiller teaches that lactulose or other fermentable substrates, including sugar alcohols such as sorbitol, should not be used for gastrointestinal lavage for colon preparation because of the risk of producing hydrogen gas in explosive concentrations in the colon. Borody *et al.* is silent with respect to including any sugar in its formulation. Hence, Borody *et al.* provides no teaching or suggestion to include a coating containing a minimally degradable sugar on a tablet form of a purgative composition. Jacob *et al.* teaches that it is well recognized in the art that the addition of appreciable quantities of substances that can be fermented by the intestinal flora should be avoided because of gas formation, which could be extremely dangerous.

Accordingly, since each of Hechter and Jacob *et al.* teaches that substances that can be fermented by the intestinal flora should be avoided in purgative compositions because of possibly extremely dangerous gas formation, and Schiller teaches that lactulose or other fermentable substrates, including sugar alcohols such as sorbitol, should not be used for gastrointestinal lavage for colon preparation because of the risk of producing hydrogen gas in explosive concentrations in the colon, there can be no suggestion or motivation to have made the modification proposed by the Examiner (*In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)), since such modification is taught by Hechter, Schiller and Jacob *et al.* to be undesirable. Thus, the teachings of the references cannot render claim 47 or any pending claim *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). Therefore, for at least these reasons, the combination of the teachings of Hechter and Schiller and Borody *et al.* and Jacob *et al.* does not teach or suggest every element of any of the pending claims.

#### **REBUTTAL TO EXAMINER'S ARGUMENTS**

The Examiner states that, although none of Hechter, Schiller Borody *et al.* and Jacob *et al.* teaches a tablet including a core containing the sodium, potassium and magnesium salts

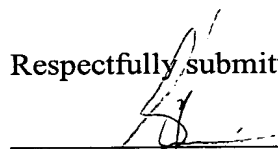
in the recited amounts and ratios, and a coating containing the minimally degradable sugar(s), it would have been a matter of routine experimentation and optimization to select a minimally degradable sugar as a coating component. The Examiner alleges that, absent evidence that the minimally degradable sugar coating of the core provides unexpected results, this modification would have been *prima facie* obvious to one of ordinary skill in the art.

Applicant respectfully disagrees. Hechter teaches that its formulations do not include organic constituents because organic constituents used in some prior art cathartics, when metabolized, can create explosive gases that have exploded during certain procedures, causing death to the patients. Schiller teaches that lactulose or sugar alcohols like sorbitol should not be used for gastrointestinal lavage for colon preparation because of the risk of producing hydrogen gas in explosive concentrations in the colon. Jacob *et al.* teaches that it is well recognized in the art that the addition of appreciable quantities of substances that can be fermented by the intestinal flora should be avoided because of gas formation, which could be extremely dangerous. Thus, routine optimization would not lead one of ordinary skill in the art to include a minimally degradable sugar in a coating of a tablet form of a purgative composition, particularly in light of the teachings of Hechter, Schiller and Jacob *et al.*

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In view of the remarks herein, entry of this amendment and allowance of the application respectfully are requested.

Respectfully submitted,



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